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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SHINYA YAMANAKA, KAZUTOSHI TAKAHASHI, and MASATO NAKAGAWA[1]

Appeal 2015-005533
Application 12/289,873
Technology Center 1600

Before DEMETRA J. MILLS, TAWEN CHANG, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims 44–52, 54–58, and 101–103 for lack of enablement commensurate with the claim scope.[2] We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] Appellants identify the Real Party in Interest as Kyoto University. App. Br. 2.

[2] We have reviewed a Decision in a related appeal, Appeal No. 2014-006588, Application Serial No. 12/379,564. The present application differs from the related Appeal No. 2014-006588 in that Appellants have not contested and appear to rely on a much earlier effective filing date for the present application. We have also reviewed our Decision in 2015-005500, Application Serial No. 13/585,729.

STATEMENT OF CASE

According to the Specification, "[t]he present invention relates to a nuclear reprogramming factor having an action of reprogramming a somatic cell to derive an induced pluripotent stem (iPS) cell." Spec. ¶ 2.

The claims are directed to a method for preparing an induced pluripotent stem cell by nuclear reprogramming of a somatic cell from a mammal, under conditions that can maintain an undifferentiated state and pluripotency of embryonic stem (ES) cells of the mammalian species, including through introducing expression vectors or recombinant vectors containing genes encoding a nuclear reprogramming factor, where the vectors encompass both retroviral vectors and non-retroviral vectors. *See, e.g.,* Spec. ¶¶ 130, 147, 175.[3]

The following claim is representative.

> 44. A method for preparing an induced pluripotent stem cell by nuclear reprogramming of a somatic cell from a mammal, which comprises contacting a nuclear reprogramming factor comprising an isolated Oct3/4 gene or gene product, an isolated Klf4 gene or gene product, and one or more isolated Myc family genes or isolated Myc family gene products of: an L-Myc gene, an N-Myc gene, and/or a c-Myc gene with the somatic cell under conditions that can maintain an undifferentiated state and pluripotency of ES cells of the mammalian species, wherein one or more pluripotent cells are obtained.

Cited References

Matthias Stadtfeld et al., *Induced Pluripotent Stem Cells Generated Without Viral Integration*, 322 Science 945 (2008) ("Stadtfeld").

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[3] *See also* Appeal Brief, pages 6–7.

Keisuke Okita et al., *Generation of Mouse Induced Pluripotent Stem Cells Without Viral Vector*, 322 Science 949 (2008) ("Okita").

Federico Gonzalez et al., *Generation of mouse-induced pluripotent stem cells by transient expression of a single nonviral polycistronic vector*, 106 PNAS 8918 (2009) ("Gonzales").

Ryan T. Rodriguez et al., *Manipulation of OCT4 Levels in Human Embryonic Stem Cells Results in Induction of Differential Cell Types*, 232 Exp. Biol. Med. 1368 (2007) ("Rodriguez").

S. Yamanaka, *Induction of pluripotent stem cells from mouse fibroblasts by four transcription factors*, 41 Cell Prolif. 51 (2008) ("Yamanaka").

vector (in biotechnology), IUPAC Compendium of Chemical Terminology, 2nd ed. (1997).

Wenbo Zhou & Curt R. Freed, *Adenoviral Gene Delivery Can Reprogram Human Fibroblasts to Induced Pluripotent Stem Cells*, 27 Stem Cells 2667 (2009) ("Zhou").

Grounds of Rejection

Claims 44–52, 54–58, and 101–103 remain rejected under 35 U.S.C. § 112, first paragraph for lack of enablement of the full scope of the claim.

FINDINGS OF FACT

The Examiner's findings of fact are set forth in the Answer at pages 2–29. The following facts are highlighted.

1. As set forth in the Appeal Brief,

> [T]he present application is a continuation-in-part that was filed on November 6, 2008. The parent application was filed on June 13, 2008 and is itself a continuation-in-part of PCT/JP2006/324881, filed December 13, 2005. The application

> also claims priority to two provisional applications with filing dates in 2007.

App. Br. 12.

2. Relevant publication dates of the cited references appear below:

> 1) Stadtfeld, et al. (Science 322 (7), 945, November 7, 2008; IDS 3/26/09, ref 99),
> 2) Okita, et al. (Science 322 (7): 949, November 7, 2008; IDS 3/26/09, ref 94),
> 3) Gonzalez, et al. (PNAS 106(22), 8918, June 2, 2009; IDS 3/13/12, ref 9).
> 4) Yamanaka (Cell Proliferation 41(Issue Suppl 1): 51, 2008; IDS 10/14/10, ref 23).
> 5) Zhou, et al. (Stem Cells 27: 2667, 2009; IDS 3/3/14, ref 4)
> 6) Fusaki, et al. (Proc Jpn. Acad., Ser B 85, 2009 (Exhibit F to Response filed on 5/23/11)
> 7) Hotta, et al. (J. Cell. Biochem. 105: 940-948, 2008; IDS, March 3, 2014, ref 2)

App. Br. 17 (Evidence Appendix).

3. The Specification states that

> [0130] There is also provided the aforementioned method, which comprises the step of adding the aforementioned nuclear reprogramming factor to a culture of the somatic cell; the aforementioned method, which comprises the step of introducing a gene encoding the aforementioned nuclear reprogramming factor into the somatic cell; the aforementioned method, which comprises the step of introducing said gene into the somatic cell by using a ***recombinant vector*** . . . . (Emphasis added.)

> [0147] In a preferred embodiment, the NRF [Nuclear Reprogramming Factor] comprises a gene product. . . . For example, the nuclear reprogramming factor can be introduced into a cell by ***transducing the cell with a recombinant vector***

comprising a gene encoding the nuclear reprogramming factor. Accordingly, the cell can express the nuclear reprogramming factor expressed as a product of a gene contained in the recombinant vector, thereby inducing reprogramming of a differentiated cell. (Emphasis added.)

[0148] The nuclear ***reprogramming*** factor may comprise a ***protein or peptide*** . . . . Further, ***by preparing and using a fusion protein with the TAT peptide derived form [sic] the virus HIV, intracellular uptake of the nuclear reprogramming factor through cell membranes can be promoted, thereby enabling induction of reprogramming only by adding the fusion protein to a medium thus avoiding complicated operations such as gene transduction. Since preparation methods of such fusion gene products are well known to those skilled in the art, skilled artisans can easily design and prepare an appropriate fusion gene product depending on the purpose.*** (Emphasis added.)

[0174] By using the nuclear reprogramming factor of the present invention, the nucleus of a somatic cell can be reprogrammed to obtain an induced pluripotent stem cell. . . . ***Methods for preparing induced pluripotent stem cells from somatic cells by using the nuclear reprogramming factor of the present invention are not particularly limited. Any method may be employed as long as the nuclear reprogramming factor can contact with somatic cells under an environment in which the somatic cells and induced pluripotent stem cells can proliferate.*** . . . . (Emphasis added.)

[0175] For example, ***a gene product contained in the nuclear reprogramming factor of the present invention may be added to a medium. Alternatively, by using a vector containing a gene that is capable of expressing the nuclear reprogramming factor of the present invention, a means of transducing said gene into a somatic cell may be employed.*** When such vector is used, two or more kinds of genes may be incorporated into the vector, and each of the gene products may be simultaneously expressed in a somatic cell. . . . It is

understood that such embodiments fall within the scope of the present invention. (Emphasis added.)

[0175] . . . Alternatively, by using a ***vector containing a gene that is capable of expressing the nuclear reprogramming factor*** of the present invention, a means of transducing said gene into a somatic cell may be employed. . . . . (emphasis added)

[0176] Specific means for using a retrovirus as a vector is disclosed in WO 2007/69666; Takahashi et al. Cell 126:663-676, 2006; and Takahashi et al. Cell 131:861-872, 2007, which are herein incorporated by reference in their entireties. Specific means for using a lentivirus as a vector is disclosed in Yu et al. Science 318: 1917-1920, 2007, which is herein incorporated by reference in its entirety. Specific means for using ***adenovirus as a vector*** is disclosed in Stadtfeld et al. (Science published online: Sep. 25, 2008, 10. 1126/science. 1162494), which is herein incorporated by reference in its entirety. Specific means for using a plasmid as a nonviral vector is disclosed in Okita et al. (Science, published online: Oct. 9, 2008, 10. 1126/science. 1164270), which is herein incorporated by reference in its entirety. ***One of ordinary skill in the art could choose and use an appropriate means from among the above known means, or from any of the other known means available in the prior art.*** (Emphasis added.)[4]

App. Br. 6–7.

4. The Specification states:

[T]he nuclear reprogramming factor of the present invention can be used to generate iPS cells from differentiated adult

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[4] Appellants appear to be relying on a Dec. 13, 2005 filing date, and therefore they cannot rely on this paragraph to support enablement, which was added after the 2005 filing date. *See,* Certified copy of the priority document of patent filed in Japan on December 13, 2005 under Patent Application No. 359537/2005, translation submitted Sept. 29, 2008.

> somatic cells. In the preparation of induced pluripotent stem cells by using the nuclear reprogramming factor of the present invention, types of somatic cells to be reprogrammed are not particularly limited, and any kind of somatic cells may be used. For example, matured somatic cells may be used, as well as somatic cells of an embryonic period. Other examples of cells capable of being generated into iPS cells and/or encompassed by the present invention include mammalian cells such as fibroblasts, B cells, T cells, dendritic cells, ketatinocytes [sic], adipose cells, epithelial cells, epidermal cells, chondrocytes, cumulus cells, neural cells, glial cells, astrocytes, cardiac cells, esophageal cells, muscle cells, melanocytes, hematopoietic cells, pancreatic cells, hepatocytes, macrophages, monocytes, mononuclear cells, and gastric cells, including gastric epithelial cells.

Spec. 51–52, ¶ 177.

5. As set forth in the Final Action, Stadtfeld, Okita, Gonzales, Yamanaka, Zhou, and Fusaki show that the delivery of reprogramming factors sufficient to reprogram somatic cells to cause them to become pluripotent was problematic when non-retroviral means for delivery was employed, and that methodology other than that disclosed by the Specification as of the effective filing date of Dec. 2005, was required. Final Act. 3–10.

6. As set forth in the Final Action, "Stadtfeld states initially attempts to reprogram mouse tail-tip fibroblasts through the introduction of Oct4, Sox2, Klf4 and c-Myc failed (Stadtfeld, page 946, col. 1, line 1 to col. 2, line 1, IDS, [11 /14/12, Ref. 580)]." Final Act. 3.

7. As the Examiner finds, Stadtfeld shows that

> [s]uccessful reprogramming occurred when adenoviral vectors comprising Sox2, Klf4 and c-Myc delivered the factors to mouse fetal liver cells and mouse tail tip fibroblasts . . . expressing Oct4 (Stadtfeld, page 946, col. 2, lines 9–13 and 17–23; and col. 3, parag. 1, lines 1–4 and 9–13). Stadtfeld [also] demonstrated reprogramming in adult mouse hepatocytes, infecting them with adenoviral vectors containing the 4 factors (Stadtfeld, page 946, col. 3, parag. 2, line 8 to page 946, col. 1, line 7). Hepatocytes, as stated by Stadtfeld, were chosen because of their natural compliance to adenovirus infection (Stadtfeld, page 946, col. 3, parag. 2, lines 1–4 and 9-13).

Final Act. 3–4.

8. Okita states they "were unable to generate iPS cells by introducing the four factors with separate adenoviral vectors." (Okita 950.) Instead, as the Examiner finds:

> Okita states the achievement of reprogramming when 3 factors (Oct4, Sox and Kl4) were delivered as a single cistronic sequence with a self-cleaving peptide in an adenoviral vector (Okita, page 950, col. 1, parag. 1, lines 1–3, 5–10 and 15–18, IDS, [11, 14, 12, Ref. 513)]. Plasmid vectors containing the same 3 factors as a polycistron were delivered on days 1 and 3. A separate plasmid vector comprising a c-Myc gene was delivered days 2 and 4 (Okita, page 950, col. 1, parag. 2, lines 1–8).

Final Act. 4.

9. Okita further discloses that, as of its publication date,

> IPS cells were first generated from mouse fibroblasts by retroviral-mediated introduction of four factors, Oct3/4, Sox2, Klf4, and c-Myc (1). Human fibroblasts can also be reprogrammed by the same four factors (2-4) or by Oct3/4, Sox2, Nanog, and Lin28 (5).

Okita, p. 949.

10. As the Examiner finds,

> Gonzales describes the delivery of a plasmid comprising Oct4, Sox2, Klf4 and c-Myc 2A-peptide linked ORFS[s] [open reading frames] by nucleofection into mouse embryonic fibroblast cells ([Gonzales], page 8921, col. 1, lines 1–8). Gonzales states 2 nucleofections were required to obtain iPSCs (Gonzales, page 8921, col. 1, parag. 2, lines 1–6, IDS, [11/14/12, ref. 340)].

Final Act. 4.

11. As set forth in the Final Action,

> Yamanaka (2008) teaches the use of a retroviral transfection system comprising nucleic acid sequences encoding reprogramming factors is indispensable for iPS cell induction (Yamanaka (2008), page 55, parag. 1, lines 4- 5, IDS, 10/14/10. Ref. 23.) While Yamanaka states other factors may induce iPSCs without a need for retroviruses, Yamanaka also states [such factors] still needed to be identified in 2008 (Yamanaka, 2008, page 55, parag. 1, lines 7-10.)

Final Act. 4.

12. As the Examiner finds,

> Zhou used an adenoviral vector to revert a somatic cell to a pluripotent state. While the adenovirus was not materially different, the method steps employed by Zhou to obtain pluripotent cells certainly were. Zhou teaches a single infection of fibroblasts with retroviral vectors separately encoding reprogramming factors did not result in any ES-like cells (Zhou, page 2671, col. 1, parag. 1, lines 9-12). Zhou teaches a protocol with multiple adenoviral vector transductions resulted in iPSC production.

Final Act. 9.

13. As the Examiner finds,

> The SeV vector taught by Fusaki to successfully induce somatic cells to a pluripotent state is materially different and separate protocol from that disclosed [in Appellants' Specification].

Final Act. 10.

PRINCIPLES OF LAW

In making our determination, we apply the preponderance of the evidence standard. *See, e.g.*, *Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office). The Board "determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction 'in light of the specification as it would be interpreted by one of ordinary skill in the art.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (quoting *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004).

> The enablement requirement ensures that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims. The scope of the claims must be less than or equal to the scope of the enablement. The scope of enablement, in turn, is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill without undue experimentation.

National Recovery Technols. Inc. v. Magnetic Separation Sys., Inc., 166 F.3d 1190, 1195–96 (Fed Cir. 1999).

An enablement rejection can be for scope of enablement or for total lack of enablement. *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999).

> [T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a

> single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

In re Fisher, 427 F.2d 833, 839 (CCPA 1970).

> [A]pplication sufficiency under § 112, first paragraph, must be judged as of its filing date. It is an applicant's obligation to supply enabling disclosure without reliance on what others may publish after he has filed an application on what is supposed to be a completed invention. If he cannot supply enabling information, he is not yet in a position to file.

In re Glass, 492 F.2d 1228, 1232 (CCPA 1974). *See also Plant Genetic Sys., N.V. v. DeKalb Genetics, Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003); *ALZA Corp v. Andrx Pharms., LLC*, 603 F.3d 935, 938, 943 (Fed. Cir. 2010) (affirming district court's determination that "claims are invalid for lack of enablement because the specification does not enable the full scope of claim 1, which covers both osmotic and non-osmotic dosage forms").

In *Alza*, "the parties agreed that the specification enables osmotic oral dosage forms, but disputed whether it also enables non-osmotic oral dosage forms." *Id.* at 938. The Federal Circuit found that "the evidence dictate[d] that a person of ordinary skill in the art would have been required to engage in undue experimentation to develop non-osmotic oral dosage forms with ascending release rates." *Id.* at 943.

ISSUE

The Examiner finds that

> Claims 44-52, 54-58 and 101-103 . . . while being enabling for a method for preparing a mammalian induced pluripotent stem cell by nuclear reprogramming of a mammalian somatic cell comprising: a) introducing into the somatic cell retroviral vectors comprising at least an Oct3/4 gene and a Klf4 gene, and at least one of l-myc, n-myc or c-myc genes each gene operably linked to a promoter; and b) culturing the transduced somatic cell under ES cell conditions, to form an induced pluripotent stem cell, does not reasonably provide enablement for a method for preparing an induced pluripotent stem cell by nuclear reprogramming of a somatic cell comprising: contacting a nuclear reprogramming factors comprising one or more isolated genes or isolated gene productions of an 1-myc gene, an n-myc gene and/or a c-myc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Final Act. 2–3. The Examiner finds that "the effective filing date of the claimed application is December 2005." (Ans. 29.)

Appellants have not proposed an alternative effective filing date for the claims on appeal. However, Appellants contend that, "[i]n the present case, the only factor weighing against the full scope of enablement of the presently pending claims is that the only working examples present in the application make use of a retroviral vector." App. Br. 6.

Appellants argue that

> "Vector" is defined by IUPAC Compendium of Chemical Terminology as "A DNA molecule (plasmid, virus, bacteriophage, artificial or cut DNA molecule) capable of being replicated and bearing cloning sites for the introduction of foreign DNA, used to introduce this DNA into host cells." A large number of such "vectors" are well known to the art and therefore, need not be disclosed in the specification in detail. Examples of such well-known vectors includes plasmids, viruses, bacteriophage, and artificial or cut DNA molecules.

> The originally filed specification discloses introduction of the genes by using such vectors. Accordingly, the description as filed duly supplies sufficient guidance for the full scope claimed.

App. Br. 7–8. Appellants contend, with respect to the references cited for showing lack of enablement at the time of filing of the application, that

> the references also do not establish that an iPSC could not be prepared by using a suitable vector prepared by one skilled in the art. In fact, Appellant respectfully submits that the references cited by the Examiner actually support the position that retroviral vectors are not required to delivery of reprogramming factors sufficient to reprogram cells which is also indicated by the Examiner in the Final Office Action.

App. Br. 8.

The issue is: Has the Examiner established a prima facie case of lack of enablement commensurate with the pending claim scope on the evidence of record? If so, have Appellants rebutted any prima facie case with argument or evidence?

ANALYSIS

We agree with the Examiner's fact finding, statement of the rejection and responses to Appellants' arguments as set forth in the Answer. We find that the Examiner has provided evidence to support a prima facie case of lack of enablement commensurate with the claim scope. We provide the following additional comment to the Examiner's argument set forth in the Final Rejection and Answer. Appellants do not argue individual claims separately, therefore we select claim 44 as representative claim.

There appears to be no dispute that the production of iPSC was nascent technology at the time of the effective filing date of the present

application. The Examiner argues that, "[s]ince the art at the time of filing (2005)[] does not provide guidance on vectors that can be used to produce iPSCs, and in view of the teachings of Stadtfeld, Okita and Gonzales, the degree of experimentation required is not routine and undue." Final Act. 12. The Examiner further argues that

> Stadtfeld et al., Okita et al. and Gonzales et al., teaches the requirement for a methodology, a methodology not disclosed by the specification, [to] obtain reprogrammed cells or iPSCs. The enablement issue is not knowledge of vectors or methods of introducing vectors to somatic cells at the time of filing, but which of the many vectors and vector varieties, and delivery protocols, would be successful in reprogramming somatic cells to pluripotency. The skilled artisan would have not been able to rely either on the prior art or the teachings in the specification to arrive at the vectors and protocols of Stadtfeld, Okita and Gonzales. Since the specification lacked such guidance, and the prior art did not provide the guidance which the specification lacked, the claims are not enabled.

Ans. 21. These references are extensively and creditably discussed by the Examiner in the Final Action and Answer, and we will not discuss them further here.

Appellants insist that

> At the priority date, one skilled in the art could choose a variety of vectors. Even if the **originally filed specification** disclosed a working example using a retroviral vector, the art will never interpret the "vector" as limited to a retroviral vector. In addition, the skilled art worker would have no difficulty optimizing the preparation of a suitable vector amongst the variety of known vectors.

App. Br. 8, emphasis added.

As the Examiner points out, however, "the issue is not knowledge of vectors of method of introducing vectors to somatic cells at the time of the filing, but which of the many vectors and vector varieties would be successful in reprogramming somatic cells to pluripotency." (Ans. 21; Final Action 7.) In other words, "the vector must deliver nucleic acids encoding nuclear reprogramming factors to somatic cells and, then, the nucleic acids delivered must be sufficient and sufficiently expressed to cause the targeted somatic cell to revert to a pluripotent state. Thus, the claims require a major physiological change to the somatic cell, one heretofore unexpected in vitro." (Ans. 8.) Thus, it is true that the present Specification ¶175 states:

> Alternatively, by using a vector containing a gene that is capable of expressing the nuclear reprogramming factor of the present invention, a means of transducing said gene into a somatic cell may be employed. When such vector is used, two or more kinds of genes may be incorporated into the vector, and each of the gene products may be simultaneously expressed in a somatic cell.

Yet, as the Examiner noted, there is also evidence of record of the failure of others to achieve pluripotent cells from non-viral vector modified somatic cells after the effective filing date of the application, and evidencing that retroviral transmission of pluripotent cells may result in tumor growth. (*See*, *e.g.*, FF9, FF10.) Moreover, the post-filing successful achievement of pluripotent cells with non-retroviral vectors was not based on routine manipulations in the production of iPS cells, as of the effective filing date. As the Examiner noted, "nothing in the production iPS cells can be considered routine at the time of Appellant's earliest filing date, December 2005, as there are no teachings in the prior art that iPS cells had been previously produced." (Ans. 6, 9–11.)

Furthermore, Appellants concede that vectors encompasses plasmids. (Appeal Br. 7–8.) Yet, there is no specific indication in the Specification as of the effective filing date of Dec. 2005, that a plasmid can successfully be used in the claimed method, or a description of a specific type of plasmid that may be used in the invention, or how to prepare such a plasmid. There is no indication in the Specification as of the effective filing date as to which and how the nuclear reprogramming factors are oriented in the plasmid. Nor does the Specification as of the effective filing date describe a specific transduction protocol for successful non-retroviral plasmid expression to obtain transformation of a somatic cell to a pluripotent stem cell. Thus, there is a lack of disclosure in Specification, as of the effective filing date, of how to effect the pluripotency of the modified somatic cell using non-retroviral vectors or plasmids, in combination with the evidence of record of the failure of some others to achieve pluripotent cells from non-viral vector modified somatic cells after the effective filing date of the application. *See Alza Corp.*, 603 F.3d at 941–943 ("Claims are invalid for lack of enablement because the specification does not enable the full scope of claim . . . .").

Appellants do not specifically respond to the Examiner's comments concerning the cited references (Ans. 19–24), which show that it was not until after the effective filing date of the present application (December 13, 2005)[5] that attempts at using non-retroviral vectors for preparing a mammalian induced pluripotent stem cell were successful. Importantly,

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[5] As discussed above, Appellants have not contested that December 13, 2005 is the effective filing date of the instant application, and appear from their arguments to be relying on this filing date. App. Br. 8, 11, Reply Br. 2, 6. Appellants make no specific argument for reliance on any other filing date than the 2005 filing date.

Appellants have not shown that one of ordinary skill in the art at the time of the 2005 effective filing date, following the disclosure of Appellants' Specification, would have been able to prepare a pluripotent stem cell from a somatic cell using a non-retroviral vector, without undue experimentation.

In particular, Appellants allege that

> Zhou et al., (Cell 27:2667-2674, 2009, IDS March 3, 2014) disclose that iPSCs were successfully produced by using an adenoviral vector. The procedure taught by Zhou did not employ any surprising technique. Rather, the procedure could be achieved with expenditure of no more effort than is normally required in the art.

App. Br. 11. Fusaki[6] was submitted by Appellants as evidence to show that vectors other than retroviral vectors could have been used for producing iPSCs. App. Br. 12.

We are not persuaded by Appellants' citations to Zhou and Fusaki. "Zhou used an adenoviral vector to revert a somatic cell to a pluripotent state." Final Act. 9. However, the method steps employed by Zhou to obtain pluripotent cells were different from those in the Specification. *Id.* The Examiner further found that "[t]he SeV vector taught by Fusaki to successfully induce somatic cells to a pluripotent state is materially different and separate protocol from that disclosed [in the Specification]." Ans. 25. Thus, that Fusaki and Zhou may exemplify post-filing successes, does not demonstrate Appellants' specification, at the time of the effective filing date, enables the claimed invention. *Accord, Enzo Biochem, Inc. v. Calgene, Inc.*,

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[6] Fusaki, N. et al., *Efficient induction of transgene-free human pluripotent stem cells using a vector based on Sendai virus, an RNA virus that does not integrate into the host genome*, 85 Proc. Jpn. Acad. Ser. B 348–362 (2009).

188 F.3d 1362, 1376 (1999) ("We also agree with Calgene that Enzo's evidence of enablement was inconclusive, as Enzo did not prove that the alleged post-filing successes were accomplished by following the teachings of the specifications."). *See also In re Wright*, 999 F.2d 1557, 1563–1564 (Fed. Cir. 1993) (holding that demonstration using one retrovirus is inadequate to enable claims to all retroviruses or even all avian RNA viruses and that undue experimentation would be required, despite the routine nature of the experimentation involved); *MagSil Corp. v. Hitachi Global Storage Technologies Inc.*, 687 F.3d 1377, 1384 (Fed. Cir. 2012) ("The record contains no showing that the knowledge of that artisan would permit, at the time of filing, achievement of the modern values above 600% without undue experimentation, indeed without the nearly twelve years of experimentation necessary to actually reach those values. . . . This court holds that the asserted claims are invalid for lack of enablement because their broad scope is not reasonably supported by the scope of enablement in the specification.")

We find that *Wyeth and Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380 (Fed. Cir. 2013) is also instructive here. *Wyeth*, as in the present case, involved a question of enablement throughout the claim scope of a method claim where only a single embodiment (use of sirolimus), of a broad claim (encompassing multiple rapamycin compounds), was disclosed in the specification. The district court below had relied "on the unpredictability of the chemical arts, the complexity of the invention, and the limited knowledge of treatment of restenosis using sirolimus at the time of the invention" in invalidating the claims at issue. *Id.* at 1384. The Federal Circuit affirmed the district court below and held in *Wyeth* that

> Here, the specification . . . discloses only a starting point for further iterative research in an unpredictable and poorly understood field. Synthesizing candidate compounds derived from sirolimus could, itself, require a complicated and lengthy series of experiments in synthetic organic chemistry. . . . The specification offers no guidance or predictions about particular substitutions that might preserve the immunosuppressive and antirestenotic effects observed in sirolimus. The resulting need to engage in a systematic screening process for each of the many rapamycin candidate compounds is excessive experimentation. We thus hold that there is no genuine dispute that practicing the full scope of the claims, measured at the filing date, required undue experimentation.

Id. at 1386. The present case, as in *Wyeth*, similarly involves the unpredictable technology of a method of converting somatic cells to induce pluripotent stem cells, despite the "art [knowing] that the nucleus of a somatic cell can be reprogrammed," that particular "nuclear reprogramming factors . . . are responsible for reprogramming a somatic cell" (Reply Br. 3), that "'vectors' are well known in the art," and that, in general, "gene transfer techniques that use vectors were well-known, common techniques in the art" (App. Br. 8). The Specification, as of the effective filing date, only enables performance of the method with retroviral vectors and provides no guidance as to manipulations required to achieve induced pluripotent stem cells with other, non-retroviral vectors within the broad scope of the claims. We agree with the Examiner that

> [s]ilence in the prior art related a particular invention or a particular aspect of an invention renders it incumbent on the disclosure to provide the necessary guidance to the skilled artisan to make and use the claimed invention. The present specification does not suggest any particular non-retroviral vector constructs, nor does the specification suggest modifications to non-retroviral vectors to enhance delivery

> and/or expression of nuclear reprogramming factor nucleic acids in somatic cells. Each successful implementation of the claimed method by the post-filing art using a nonretroviral vector, used a vector and/or method not disclosed by or supported by the specification. From this, reprogramming somatic cells to an earlier undifferentiated, pluripotent states ranks among nascent inventions. MPEP states "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art.["]

Ans. 9–10. The Examiner further finds that even if the skilled artisan would have known how to optimize the particular non-viral vector to use in the claimed method, at the time of the invention, it would have required undue experimentation to produce a non-retroviral vector capable of inducing pluripotency in a somatic cell. Final Act. 11; Ans. 9–14. We conclude that practicing the full scope of the claims, measured at the filing date, required undue experimentation.

We agree with the Examiner that claims 44–52, 54–58, and 101–103 do not enable the full scope of the claim, and the 35 U.S.C. § 112, first paragraph rejection of the claims for lack of enablement is affirmed for the reasons of record.

DECISION

We affirm the lack of enablement rejection of claims 44–52, 54–58, and 101–103 for the reasons of record. The cited references, and preponderance of the evidence, support the Examiner's lack of enablement rejection. Arguments not made are waived.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED